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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/256,156	02/24/1999	STEPHEN GILLIES	LEX-003	9492

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EXAMINER

KAPUST, RACHEL B

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 07/14/2003

26

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/256,156

Applicant(s)

GILLIES ET AL.

Examin r

Rachel B. Kapust

Art Unit

1647

-- The MAILING DATE of this communication appears on th cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4,6-24 and 26-28 is/are pending in the application.
- 4a) Of the above claim(s) 14-24 and 26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,6-13,27 and 28 is/are rejected.
- 7) ☒ Claim(s) 4 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Art Unit: 1647

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647.

Claims 1 and 27 were amended in Paper No. 23 filed on January 29, 2003, and claim 28 was added in Paper No. 24 filed on April 23, 2003. Claims 1-4, 6-24, and 26-28 are pending. Claims 14-24 and 26 stand withdrawn from consideration pursuant to 37 CFR § 1.142(b). Claims 1-4, 6-13, 27, and 28 are under consideration.

Response to Amendment

The rejection of claims 2 and 27 under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, has been withdrawn based on Applicant's arguments.

The rejection of claims 1, 3, 6-9, and 13 under 35 USC § 102(b) as being anticipated by Hoogenboom *et al.* (1991) has been withdrawn based on Applicant's arguments.

Information Disclosure Statement

The information disclosure statement filed April 29, 2003 has been placed in the application file, but the information referred to therein has not been considered as to the merits. Because the information disclosure statement was just recently received, the information is not yet available for review. The information will be considered as soon as it becomes available.

Specification

The disclosure is objected to because of the following informalities: Figures 1, 2, and 6 contain amino acid or nucleic acid sequences. Applicants are directed to 37 C.F.R. § 1.821(d)

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In order to comply with 37 C.F.R. 1.821, appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 8, and 13 are rejected under 35 USC § 112, second paragraph. Claim 7 recites the limitation "said second non-Ig protein" in reference to the antibody-based fusion protein of claim 1. Claim 1 is drawn to an antibody-based fusion protein linked to a non-Ig protein. As written, there is only one non-Ig protein in claim 1, therefore there is no antecedent basis for a second non-Ig protein.

Claim 8 recites the limitation "said cytokine" in reference to the antibody-fusion protein of claim 1. However, claim 1 does not refer to a cytokine. Similarly, claim 13 recites the limitation "said ligand-binding protein" in reference to the antibody-based fusion protein of claim 1. Claim 1 does not refer to a ligand-binding protein. There is insufficient antecedent basis for these limitations in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, and 6-10 are rejected under 35 U.S.C. § 102(a) as being anticipated by Junghans, International Publication No. WO 97/43316. Junghans teaches fusion proteins with extended half-lives wherein the fusion proteins comprise a physiologically active molecule fused to another that encodes an amino acid sequence capable of binding to the FcRp (p. 11, lines 25-34). As in claim 1, Junghans teaches that the domain that is required for binding to FcRp is necessary for extending the half-life of the physiologically active molecule. More specifically, Junghans teaches fusion to immunoglobulins such as IgG1 wherein the Fc region is modified so that it does not bind to an Fc receptor (p. 3, lines 8-19 and p. 19, line 21 through p. 20, line 4). In regard to claim 3, Junghans teaches that when mutations are made at positions Leu₂₃₄ and Pro₃₃₁ within an IgG Fc domain, IgG binding to FcRI is abolished (p. 7, lines 9-11). Referring to claim 6, Junghans teaches that modification of the Fc region can be done by making deletions/mutations within the CH2 domain to delete the binding for Fc receptors such as FcRI, FcRII, and FcRIII (p. 7, lines 4-9). In regard to claims 7-10, Junghans teaches that examples of physiologically active molecules that can be used in the antibody-based fusion proteins are TGFβ, IgM, and cytokines such as IL-1, IL-2, IL-12, IFNγ, TNF, Duffy binding proteins, and p85 (p. 12, lines 4-19). Thus, the claim limitations are met, and the claims are anticipated.

Art Unit: 1647

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claim 2 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Junghans as applied to claims 1, 3, and 6-10 above, and further in view of Xu *et al.* (1994) *J. Biol. Chem.* 269: 3469-3474. Junghans teaches antibody-based fusion proteins comprising at least a portion of a CH2 domain linked to a non-Ig protein. Junghans further teaches that the half-life of the antibody-based fusion protein can be enhanced by having regions that are capable of “binding to the FcR β to thereby take advantage of its protective effects but do not bind to an Fc receptor which mediates immune effects” (see p. 6, lines 23-29). Modification of the Fc region of IgG, for example IgG1, is contemplated by Junghans (see p. 19, lines 29-30). Moreover, Junghans teaches making deletions/substitutions/mutations within the CH2 domain to delete the binding for FcRI, FcRII, FcRIII, and complement (p. 7, lines 4-9). However, Junghans does not teach

Art Unit: 1647

the utilization of an IgG2 CH2 domain whereby the half-life of the antibody-based fusion protein is longer than when an IgG1 CH2 domain is used.

Xu *et al.* teach that IgG1 and IgG3 are the most efficient at binding and activating C1, IgG2 is significantly less active, and IgG4 is inactive (p. 3469, column 1). In addition, Xu *et al.* teach that the C1 binding domain is located in the IgG CH2 domain (p. 3469, column 2). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to utilize a portion of the CH2 domain of IgG2 instead of a portion of the CH2 domain of IgG1, because IgG1 has a greater affinity for complement than IgG2. Junghans specifically teaches making mutations/substitutions/deletions in order to decrease or eliminate the binding to complement.

Claim 3 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Junghans as applied to claims 1, 3, and 6-10 above, and further in view of Winter *et al.*, U.S. Patent No. 5,624,821. Junghans teaches that when mutations are made at positions Leu₂₃₄ and Pro₃₃₁ within an IgG Fc domain, IgG binding to FcRI is abolished (p. 7, lines 9-11). However, Junghans does not teach mutations or deletions at positions Leu₂₃₅, Gly₂₃₆, or Asn₂₉₇ within the IgG1 constant region. Winter *et al.* teach that modifications at positions Leu₂₃₄, Leu₂₃₅, Gly₂₃₆, and Asn₂₉₇ will alter an effector function of an IgG as compared with unmodified antibody (see column 5, lines 42-58; column 7, lines 21-28; and claim 1). One of ordinary skill in the art would have been motivated to make modifications at positions Leu₂₃₅, Gly₂₃₆, and Asn₂₉₇ in order to negatively affect the binding to FcRI and thereby increase the half-life of the antibody-based fusion protein. Thus, it would have been obvious to a person of ordinary skill in the art to make an antibody-

Art Unit: 1647

based fusion protein wherein the CH2 domain has a mutation or deletion that reduces the binding affinity for an Fc receptor, and the mutation or deletion occurs at either Leu₂₃₄, Leu₂₃₅, Gly₂₃₆, Asn₂₉₇ or Pro₃₃₁.

Claims 11-13 and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Junghans as applied to claims 1, 3, and 6-10 above. Claims 11-13 and 28 are drawn to antibody-based fusion proteins wherein the non-Ig protein is either a lymphokine, a colony stimulating factor, a ligand-binding protein or an interleukin receptor. While Junghans does not teach these exact examples of fusion partners, Junghans does teach that examples of physiologically active molecules that can be used in the antibody-based fusion proteins are TGF β , IgM, and cytokines such as IL-1, IL-2, IL-12, IFN γ , TNF, Duffy binding proteins, and p85 (p. 12, lines 4-19). More importantly, it is common for one of ordinary skill in the art to engineer fusion proteins comprising in part a heterologous protein (see for example U.S. Patent No. 5,679,543; U.S. Patent No. 5,349,053; and U.S. Patent No. 5,314,995 ('053 and '995 submitted by Applicants in the supplemental IDS, paper no. 25)). In regard to claims 11-13, specific examples of recombinant antibodies fused to either a cytokine, lymphotoxin, TNF α , IL-2, or granulocyte-macrophage colony stimulating factor can be found in Gillies, U.S. Patent No. 5,650,150 (submitted by Applicants in the supplemental IDS, paper no. 25). In regard to claim 13, Batra *et al.* (1993), *Mol. Immunol.* 30: 379-386 teach the insertion of various portions of the constant domain of human IgG1 into CD4-PE40, a recombinant toxin, in order to increase the half-life of the toxin.

Art Unit: 1647

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute any physiologically active molecule in the fusion protein taught by Junghans. More specifically, it would have been obvious to one of ordinary skill in the art to substitute any of the proteins taught by Gillies et al. (1993), Gillies in U.S. Patent No. 5,650,150, or Batra et al. (1993) in the fusion protein taught by Junghans.

Claim 27 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Junghans and Xu *et al.* as discussed above, and further in view of Harvill *et al.* (1995), Immunotech. 1: 95-105. Junghans teaches that a mutation or deletion within the CH2 domain of the antibody-based fusion protein that deletes the binding affinity for an Fc receptor or complement is beneficial for increasing the half-life of the fusion protein. Xu *et al.* teach that the CH2 domain of IgG4 has no affinity for FcRI whereas IgG1 has a high affinity for the receptor. Since Junghans teaches the benefits of having a decreased affinity for Fc receptors, one of ordinary skill in the art would have been motivated to use the CH2 domain of IgG4 as opposed to the CH2 domain of IgG1. Neither Xu *et al.* nor Junghans specifically teach an antibody-based fusion protein wherein the C-terminus of the protein comprising a portion of a CH2 domain is linked to the N-terminus of a non-Ig protein. However, Harvill *et al.* teach a fusion protein wherein the N-terminus of a non-IgG protein is fused to the C-terminus of IgG3. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have the fusion occur at the N-terminus of the non-IgG protein as opposed to the C-terminus of the non-IgG protein.

Accordingly, the invention taken as a whole is *prima facie* obvious over the prior art.

Art Unit: 1647

Allowable Subject Matter


Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (703) 305-0634.

The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 892-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


RBK
July 10, 2003